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NOTICE OF ALLOWANCE AND ISSUE FEE DUE

18N2/0711

STERNE KESSLER GOLDSTEIN
SUITE 600
1100 NEW YORK AVENUE NW
WASHINGTON DC 20005-3934

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/249,671	05/26/94	016	FITZGERALD, D 1812	07/11/97

First Named Applicant: HAUPTMANN, RUDOLF

TITLE OF INVENTION: PROCESS AND VECTOR FOR EXPRESSING ALPHA-INTERFERON IN E. COLI (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 0652.1350000	435-069.510	P22	UTILITY	NO	$1290.00	10/14/97

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

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III. All communications regarding this application must give application number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/249,671	05/26/94	HAUPTMANN	F [illegible]

EXAMINER	
FITZGERALD,D	
ART UNIT	**PAPER NUMBER**
1812	22/E

DATE MAILED: 07/11/97

18N2/0711
STERNE KESSLER GOLDSTEIN & FOX
SUITE 600
1100 NEW YORK AVENUE NW
WASHINGTON DC 20005-3934

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

NOTICE OF ALLOWABILITY

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to Amdt 27 June 1997; Interview 10 July 1997

☒ The allowed claim(s) is/are 1, 3-9, 17, 19-21, 24, 28-30; to issue as 1-8, 12-16, & 28-30, respectively

☒ The drawings filed on 26 May 1994 are acceptable.

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS FROM THE "DATE MAILED"** of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Interview Summary, PTO-413

☒ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

EXAMINER'S AMENDMENT

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee. Authorization for this Examiner's Amendment was given in a telephone interview with Robert Esmond on 10 July 1997.

In the claims:

Claim 9, line 1, delete "comprising" and replace it with — comprises — .

Following the claims, insert the following abstract:

— Abstract of the Invention

Methods and vectors for expressing interferon-alpha (IFN-α) proteins in *E. coli* are provided. Use of a vector comprising an IFN-α sequence fused to an *E. coli* heat-stable enterotoxin signal sequence (*STII*) under the control of the *E. coli* phosphatase (*phoA*) promoter affords high levels of correctly-folded and -processed, biologically active IFN-α polypeptides. —

The title is amended by the examiner as follows (M.P.E.P. § 606.01):

Process [~~for Preparing and Purifying~~] and Vector for Expressing Alpha-Interferon in *E. coli* .

REASONS FOR ALLOWANCE

The following is an Examiner's Statement of Reasons for Allowance. Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably **accompany** the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

The two declarations under 37 C.F.R. § 1.132 filed 27 June 1997 are sufficient to overcome the outstanding rejections under 35 U.S.C. § 103. Together, the declarations provide

simplifying the issues. Finally, the Amendment is necessary to more clearly identify the subject matter claimed by the Applicants. The Amendment was not made earlier as it was necessitated by the Examiner's remarks in the outstanding Office Action.

Upon entry of the foregoing Amendment, claims 1, 3-9, 17, 19-21, 24, and 28-30 are pending in the application, with claims 1 and 17 being the independent claims. Claims 25 to 27 have been canceled in response to the Examiner's assertion that the subject-matter of these claims is identical in scope and content to that in claims 1, 8 and 9, respectively. Claims 28 to 30 have been amended such that they now depend from claims 1 and 8, rather than claims 25 and 26.

Applicants also respectfully request that the Examiner consider the two Declarations filed herewith under 37 C.F.R. §1.132.

The first Declaration, filed unsigned with the previous Amendment and Response, November 18, 1996, is herewith re-submitted executed in original. The Second Declaration under 37 C.F.R. §1.132 is herewith submitted in response to the Examiner's request for "a declaration comparing results obtained with the instant invention with those of the prior art on a units-per-liter basis" (present Office Action, page 4, lines 28-29). As this particular suggestion was only made in the present Office Action, it would have been impossible for the Applicants to have submitted earlier a Declaration to this effect.

I. Request for Re-submission of the Original Claims Pages

The Examiner has requested that the Applicants again submit duplicates of the original claims, pages 37-41 of the application as filed, in order to ensure that these pages are legible and

the record is complete. The replacement pages currently in the file were requested in a telephone call from Gloria Trammel of Group 1800 on February 29, 1996. On this date, Ms. Trammel informed the undersigned attorney that the original copy of the claims had been separated from the file. The duplicate pages submitted herewith are in fact identical to those in the application as filed.

II. Objection as to Duplicate Claims have been Overcome by Amendment

The Examiner has objected to claims 1 and 8 as being identical in scope and content to claims 25 and 26, respectively. In addition, The Examiner has objected to claims 9 and 27 as being substantially identical to each other.

Applicants have canceled claims 25-27 in response to this objection. In light of this amendment, Applicants respectfully request that this objection be withdrawn.

III. Rejection under 35 U.S.C. § 112

The Examiner has rejected claim 27 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

Applicants have canceled claim 27. Applicants submit that cancellation of this claim renders the rejection moot. Withdrawal of the rejection is respectfully requested.

IV. The Claimed Invention is Not Obvious Over the Prior Art

The Examiner in the present Office Action maintains the following rejections under 35 U.S.C. §103, each of which were set forth in the previous Office Action (Paper No. 14, mailed May 16, 1996):

[¶ 5] Miyake (JB, 1985) in view of Chang ('165), Vandlen ('060), Capon ('165), and Baxter ('287), applicable to claims 1, 3, 17, 19, 25, and 30.

[¶ 6] Miyake in view of Chang, Vandlen, Capon, and Baxter, further in view of Hauptmann ('887), applicable to claims 8, 9, 20, 21, 24, and 26-29.

[¶ 7] Miyake in view of Chang, Vandlen, Capon, and Baxter, further in view of Protasi ('786) and Higashi ('990), applicable to claims 4-7.

Applicants respectfully traverse these rejections. Applicants reiterate and incorporate by reference the remarks presented in the Amendment and Response filed November 18, 1996 as they relate to the above rejections.

In the present Office Action, the Examiner states that he does not agree with Applicants' assertion that Chang "teaches away" from the invention as claimed. Further to this argument, Applicants respectfully remind the Examiner that prior art references must be considered in their entirety, including disclosures within the reference that teach away from the claims of the application under consideration. "A prior art reference must be considered in its entirety, i.e., as a *whole*, including portions that would lead away from the claimed invention." MPEP 2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The Examiner has suggested, quoting Chang '495, col. 6, ll. 19-29 ("[t]he prokaryotic signal sequences to be used herein is the signal sequence from

any bacterial secreted or cell membrane protein. . . . Of the ST enterotoxins, STII is most preferred"), that this reference teaches toward the present invention. Applicants respectfully submit that this document when taken as a whole must be viewed as teaching away from the present invention.

Specifically, Applicants call attention once again to Chang *et al.* at col. 8, ll. 26-34, "[T]he promoter does not appear to affect the proportion of eukaryotic protein that is secreted. However, it is desirable to screen combinations of promoters and signal sequences for optimal expression since both elements interact in affecting expression levels." The Examiner may be correct in his evaluation that the "proportion" referred to here is (amount of IFN secreted) ÷ (total amount of IFN produced), not simply the gross amount of IFN recovered (present Office Action, page 4, lines 9-11). Applicants submit, however, that this interpretation is consistent with Applicants' position that the invention is not *prima facie* obvious. It has been discovered that the choice of promoter is particularly important in determining the proportion of properly processed and secreted IFN-α2c. As explained in the Second Declaration by Dr. Hauptmann (¶ 6), appended hereto, Voss *et al.*, Exhibit C, in Figure 3 demonstrate clearly that the proportion of IFN-α2c that is secreted and appropriately processed is significantly affected by the promoter and signal sequence. In fact, the only combination of promoter and signal sequence which led to the production of a detectable amount of correctly processed IFN-α2c is the phoA promoter coupled with the STII signal sequence, as shown in lane 2 of Figure 3. This is the exact combination that is claimed for use in the present invention. Thus, Applicants' invention is contrary to the specific teachings of Chang *et al.*

Further, Applicants respectfully submit that the cited references, when considered alone or in the combinations specified, do not suggest the claimed invention. Rather, Applicants assert

that the Examiner has improperly combined the references from the prior art, using hindsight reconstruction to choose the appropriate promoter and signal sequence for optimal expression and secretion of IFN-α, without evidence to support the combination and in the face of contrary teachings in the prior art. An artisan of ordinary skill, in light of the prior art taken as a whole, would find nothing to suggest that the expression of correctly processed IFN-α would only be possible by the combination of the phoA promoter and the signal sequence from STII.

The art is empirical (Chang *et al.*, column 5, ll. 36-68), as pointed out by the Examiner in the previous Office Action (Paper No. 14, mailed May 16, 1996). Each promoter-signal sequence combination yields a different result when coupled with a different eukaryotic passenger protein. However, the combined teachings of the cited prior art do not suggest that combining the phoA promoter with the STII signal sequence will lead to high levels of IFN-α expression and its secretion and processing. Therefore, the Applicants submit that the Examiner here merely "presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings." *In re Dow Chemical*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

Even assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicants submit that the unexpected results achieved by Applicants' claimed invention overcome any basis for *prima facie* obviousness that the Examiner may assert.

In the present Office Action, the Examiner states that the critical comparison is between the AP/AP combination, as employed by Miyake, and the AP/STII combination, as in the claimed invention. A direct comparison of the results of these promoter-signal sequence combinations has now been made. Applicants direct the attention of the Examiner to the Second

Declaration of Dr. Rudolf Hauptmann, appended hereto. At the request of the Examiner, the units used to report this comparison have been standardized to interferon units/50 OD/liter. Reported in this fashion, with the current invention "when IFN-α was expressed from *E. coli* HB101 containing the AP/STII/IFN-α construct . . . the yield of IFN-α obtained from this construct (5 to 10 mg/50 OD/liter) corresponds to 1.15 to 2.3 x 10^9 units/50 OD/liter." (Second Declaration, page 2, ¶ 5.) It is clear that this result is significantly higher (1.5 x 10^4 to 2.9 x 10^5 times) than that reported in Miyake (7.6 to 8.0 x 10^3 units/50 OD/liter). This "significantly exceed[s] the expected *ca.* 5-fold enhancement of recovery compared to the results disclosed by Miyake *et al.*" (present Office Action, page 4, ll. 24-26). The above direct comparison demonstrates that the joining of the phoA promoter with the STII signal sequence to control the expression and secretion of IFN-α results in a significant and unexpected increase in the level of protein production and secretion over that which might have been expected in view of Miyake *et al.* In light of the Second Declaration under 37 C.F.R. § 1.132 and remarks above, Applicants request that the Examiner withdraw the rejections under 35 U.S.C. § 103.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the current application is in condition for allowance. If the Examiner believes, for any

reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond

Robert W. Esmond
Attorney for Applicants
Registration No. 32,893

Date: June 27, 1997

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005
(202) 371-2600

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